Layman's Abstract
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Phase I Trial of Adenovirus-Mediated IL-12 Gene Transduction in Patients with Radiorecurent Prostate Cancer

Radiation therapy is a common therapy for men with clinically localized prostate cancer. However, this treatment fails in many men, especially those with aggressive pathological characteristics or high tumor burden as inferred by serum PSA levels >10. These patients have few viable treatment options. Salvage therapies including surgery, radioactive seed implantation and cryotherapy have high failure rates due to the presence of locally extensive disease and/or the presence of undetected metastatic disease and often debilitating side effects. Most patients are treated with some form of hormone therapy, a non-curative treatment. We have been exploring the use of cytokine gene therapy to stimulate both local and systemic grow effects without the toxicity associated with intravenous delivery of recombinant cytokines. In a mouse model of prostate cancer adenovirus -mediated (Ad.) transduction of the cytokine IL-12 (Ad.mIL-12) resulted in local growth suppression to result in marked survival enhancement and inhibition of metastases. Growth suppression was directed by both a Natural killer and T cell immune response and via increased expression of a surface marker called Fas. Interaction of Fas with another cellular marker,FasL which is expressed by immune cells and other tissues, results in cell kill. On the basis of these results, we propose to explore the use of Ad.hIL-12 in patients with clinically localized radiorecurrent prostate cancer in a Phase I trial. Patients will be placed in escalating dose cohorts with the primary endpoint of learning the maximum dose that can be safely given by an injection directly into the prostate. Toxicity will be determined through physical examination, laboratory values and serum levels of pro-inflammatory cytokines. Correlation of the immune response noted in the mouse model will be achieved by assaying for NK and T cells within peripheral blood mononuclear cells (PBMCs). NK cells extracted from PBMCs will be screened for the ability to kill NK-sensitive versus -insensitive targets, comparing cells obtained prior to and at various time points after Ad.hIL-12 therapy. Likewise, T cells from PBMCs will be screened for activity against the prostate antigens PSA and PAP. Comparisons will be drawn from reactions pre- and post-Ad.hIL-12 injection. Lastly, evidence of efficacy will be suggested from monitoring of serum PSA. In summary this trial is designed for patients with few viable options to test the safety of Ad.hIL-12 therapy and correlate with endpoints defined in an animal model.